## ABSTRACT

Provided is a method of identifying binding sites on a macromolecule comprising: **(a)** for at least one organic fragment (ORF), conducting, at separate values of parameter *B*, two or more simulated annealing of chemical potential calculations using the ORF as the inserted solvent; and **(b)** comparing converged solutions from step (a) to identify first locations at which the relevant ORF is strongly bound, thereby identifying candidate sites for binding ligand molecules.